REMARKS

Support for the amendments to Claim 61, can be found, *inter alia*, at page 5 and Figure 7B of the present specification. At page 5, it is taught that "In a further embodiment, the isolated nucleic acid sequence comprises a sequence with at least 90% and most preferably 100% in the evolutionary conserved domains described in Figure 7". Figure 7B shows the evolutionary conserved sequences in homology domain 1, which sequence is shown in SEQ ID NO:24; and the evolutionary conserved sequences in homology domain 2, which sequence is shown in SEQ ID NO:25.

Hence, the amendments to Claim 61 do not constitute new matter, and thus entry is respectfully requested.

On page 2 of the Office Action, the Examiner states that there is no amino acid sequence identifier depicting the amino acid sequence in Figure 2 or under the nucleotide sequence of SEQ ID NO:1.

Accordingly, Applicants file herewith a Substitute Sequence Listing as per the Examiner's request, adding a sequence identifier (SEQ ID NO:23) for the amino acid sequence alone.

Applicants note, the Examiner states that in Venter et al, SEQ ID NO:3129 is identical to residues 6-1429 of the amino acid sequence encoded by the nucleotide sequence of SEQ ID NO:1 of the present application. The Examiner also states that the C-terminal amino acids of Applicants' sequence shows that these amino acids correspond to the C-terminal of Venter et al's SEQ ID NO:3129. That is, a string of amino acids N-terminal of residues of 1464 of SEQ ID NO:1 is the same as Venter et al's amino acid N-terminal to residue 1429.

However, the Examiner contends that there is a discrepancy of 40 amino acids (5 at the N-terminal of SEQ ID NO:3129 and 40 somewhere in between the N and C-terminal of Applicants' amino acid sequence).

The Examiner is requested to note that Venter et al Lgs-Protein has a 5 amino acid longer N-terminus (Met-Leu-Ser-Thr-Thr) before the Lgs protein sequence, start sequence (Met-Pro-Arg-Ser-Pro...), of the present application. This difference is due to an alternative ATG-start codon in frame with the ATG-start codon used by Applicants.

Initiation of translation starts at the so-called start codon which is ATG and encodes for Methionine. It is well-known that such start codons are flanked by conserved nucleotides that probably serve as signal for the translation machinery.

The sequence in vertebrates flanking a translation start is known as a Kozak-consensus sequence (Kozak, *Nucleis Acid Research*, 15(20) (1987)).

In Drosophila, however, this conserved sequence is slightly different and known as the Cavener-consensus sequence (Cavener, *Nucleic Acid Research*, 15(4) (1987)).

Whether one applies Kozak or Cavener, in any case, it is the flanking region of Applicants, not the Venter-start codon

which resembles the Cavener/Kozak consensus sequence (see Table below).

	-6	-5	-4	-3	-2	-1	Start Codon	+1
Translation Initiation site by Venter et al	T	C	T	A	G	G	ATG	C
Kozak-consensus	G	C	C	A/G	C	C	ATG	G
Cavener-consensus			A/C	A	A	A/C	ATG	
Overlap		✓		✓				
Translation initiation site by Applicants	A	C	A	A	C	A	ATG	C
Kozak-consensus	G	C	C	A/G	C	C	ATG	G
Cavener-consensus			A/C	A	A	A/C	ATG	
Overlap		✓	✓	✓	✓	✓		

Applicants believe that it is more likely that the cloned ATG-start codon is the one that is more often used as translation initiation than the Venter et al ATG-start codon because it has a higher consensus with both the Kozak- and the Cavener-sequence, respectively. For this reason, Applicants' protein sequence starts with the recited ATG-start codon.

In addition, in the Venter et al Lgs-protein sequence, 40 amino acids are missing compared to the sequence described in the present application. Applicants believe that the Venter et al sequence is wrong in this respect for two reasons:

(1) These "additional" 40 amino acids have in the meantime been confirmed by publicly available sequences, as e.g.:

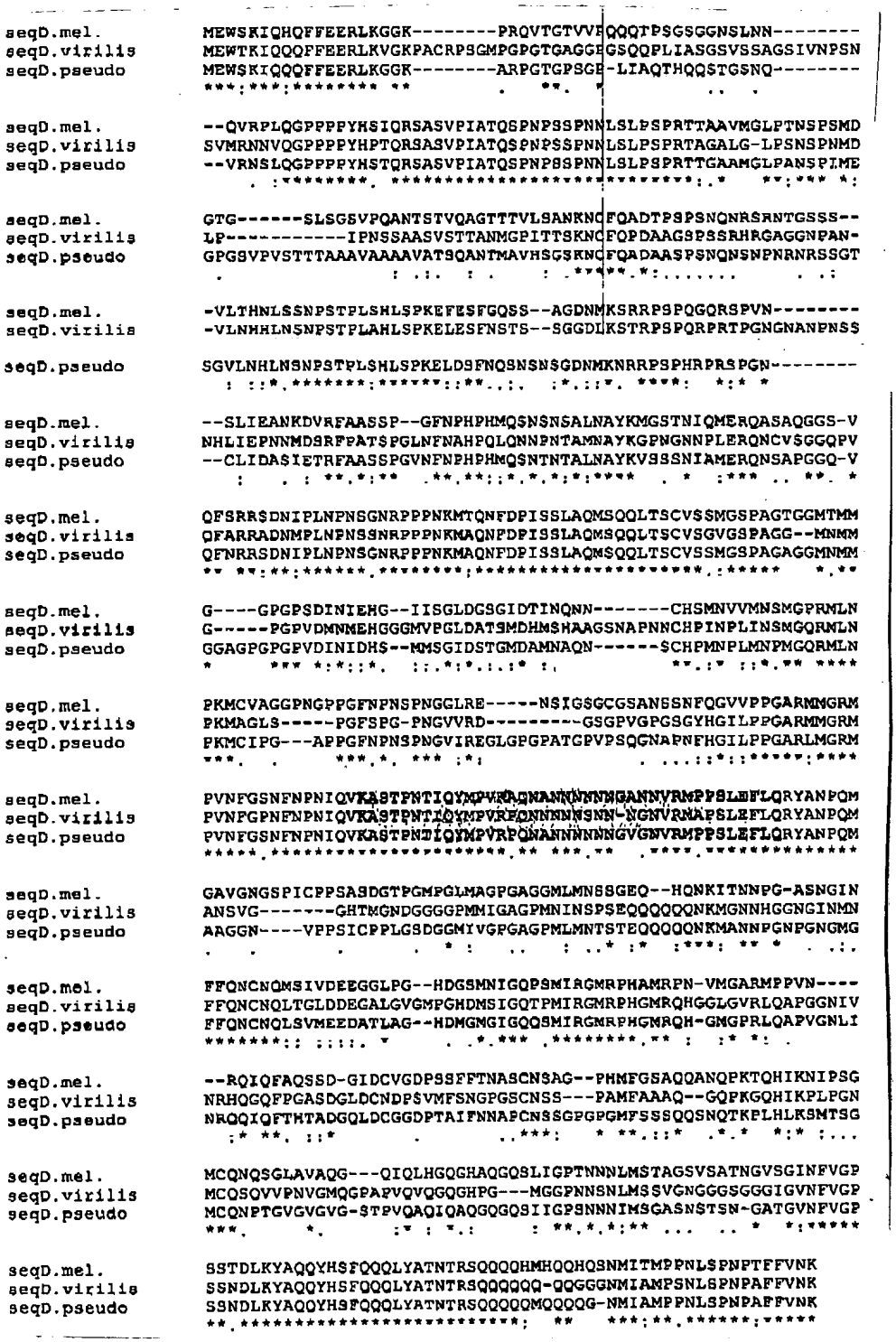
http://www.ncbi.nlm.nlh.gov/entrez/viewer.fcgl?db=nucleotide&val=15291612

(2) Furthermore, an alignment of the Legless proteins of three Drosophilae, namely *D. melanogaster*, *D. virilis* and *D. psuedoobscura*, reveals that this stretch of 40 amino acids is highly conserved and present in all three strains (see yellow stretch in the ClustalW alignment shown below). It is

therefore very likely that the Legless protein of Drosophila melanogaster contains those 40 amino acids, as shown in the present application.

CLUSTAL W (1.82) multiple sequence alignment

```
seqD.mel.       MLSTTMPRSPTQQQPQPNSDASSTSASGSNPGAAIGNGDSAASRSSPKTLNSEPFSTLSP
seqD.virilis    MLSATTGGVSQSSPTNPD------------------GANKIDGLKTVKVKTEPFSTLSP
seqD.pseudo     MLSTTMPVSPAQAQTQANVDTSTSASSVG-----IGIGIGSPKSDPFSTVSPDQTKAMSD
                ***:*    . .  .:.:                 * .  .     .:..:  .::*

seqD.mel.       DQIKLTPEEGTEKSGLSTSDKAATGGAPGSGNNLPEGQTMLRQNSTSTINSCLVASPQNS
seqD.virilis    ASALRQN-------------------------------------LSNNSANSPPNNAGDHS
seqD.pseudo     DASEKNGVPKNGKDVIAASGSASGVGNGSSGTGTADGQPSS-SVGSSSINSCLIASPNNT
                                                          ...: **    : :::

seqD.mel.       SEHSNSSNVSATVGLTQMVDCDE------QSKKNKCSVKDEEAEISSNKAKGQAAGGGCE
seqD.virilis    NTNSNSSNSNNSGSLSQRVNSEGDLHPEDLLKKKKSSAKDEDFSGNNS-----SGGVGSS
seqD.pseudo     SEHSNSSNVSAVAALAQMGDSDLGQSQEEHSKKKKMLVKDEDAEKASNKAKGLGSGAGSG
                . :***** .   .*:*  :.:          **:*  .***: .  ..     ..* *.

seqD.mel.       TG----STSSLTVKEEPTDVLGSLVNMKKEERENHSPTMSPVGFGSIG----NAQ-DNSA
seqD.virilis    NTKVGAAAAANAVKEEPSDLLGSLGNMKKED--NFSPSMSPVGFGSIGGPSGNIGPDRSV
seqD.pseudo     SGPGSGLNATVAIKEEPADVLTSLVNVKKEE--NHSPNMSPVGFGSIGGRSGNTQ-ESVV
                .       :: ::*****:*:* ** *:***:  *.**.**********     *   :  .

seqD.mel.       TPVKIERISNDSTTEKKGSSLTMNNDE-MSMEGCNQLNPDFINESLNNPAISSILVSG--
seqD.virilis    TPVKMELSSNITEKPSSIMGLSSENDIGGCNALVNSLDADRMNDANASNSNITGGPVGGP
seqD.pseudo     TTVKMELNVGSSSSEKTTTALNTDEMGGMGGIVCNHLSSDLMSETSNSTPGSSGVALN--
                *.**:*   . : . ..  .*. ::         * *..* :.::  . .  :    .

seqD.mel.       --VGPIPGIGVGAGTGN-----LLTANANGISSGSSNCLDYMQQQNHIFVFSTQLANKGA
seqD.virilis    AGSGPGLGVSLGIGINVSPGASNFMGGNNSVGNALGNCLDYMQQQNHIFVFSTQLANNGA
seqD.pseudo     --MNAPHATPGGAGCVVGVGNLMAGNGGTSIGVGVGNCLDYMQQQNHIFVFSTQLANKGA
                  ..  .   * *              . ..:. . .********************:**

seqD.mel.       ESVLSGQFQTIIAYHCTQPATKSFLEDFFMKNPLKISKLQRHNSVG-----MPWIGMGQV
seqD.virilis    ESVLSGQFQTIIAYHCTQPATKSFLEDFFMKNPMKMNKLQRQNSLGLGICNMPGPGGGQS
seqD.pseudo     ESVLSGQFQTIIAYHCTQPATKSFLEDFFMKNPMKMSKLQRQSSLG-----IPWMGIVPG
                **********************************:*:*****:.*:*     :*  *

seqD.mel.       GLTPPNPVAKITQQQPHTKTVG-----LLKPQFNQHENSKRSTVSAPSNSFVDQ------
seqD.virilis    WLNPNANSNNNLNPNPNSNPNLAKILQSQQKPGVAAAAGPKSHFNSQADNSSNKRNAFAD
seqD.pseudo     IATTGPNLVSKLSQQPTPQSKSSGSLQRSQAQFNQSDNSKRNAMNAPSSNYADQ------
                  ..     .  . :* .:.          :        . :. ..: :..  ::

seqD.mel.       ---SDPMGNETELMCWEGGS---SNTSRSGQNSRNHVDSISTSSESQAIKILEAAGVDLG
seqD.virilis    PSPADSLVNDSDLMCWETANANQSAVNRNSLDGAQG----TAASESHAMKLMEGS---VD
seqD.pseudo     ---TDTLN-ENDLMCWESGAGAGGTGSGSGPNSRNNNESCNGPNESQAIKLLEAAGVDLG
                   :*.:  :.:***** .    .  . .. :. :   . ..**:*:*::*.:    :.

seqD.mel.       QVTKGSDPGLTTENNIVSLQGVKVPDENLTPQQRQHREEQLAKIKKMNQFLFPENENSVG
seqD.virilis    SVLGKCNSDLSTDNNIISLQGVKVPDENLTPQQRQHREEQLAKLKKMNQFLFPEQDSGPG
seqD.pseudo     QGKS-NDLNLSHENNIISLQGVKVPDENLTPQQRQHREEQLAKIKKMNQFLFPENDTGSG
                .     : .*: :***:**********************:**********:.. *

seqD.mel.       ANVSS--QITKIPGDLMMGMSGGG----GGSIINPTMRQLHMPGNAKSELLSATSSGLSE
seqD.virilis    Q-------LNKLPNDSAMGSIMMSMPGGGATNAQMRQMQLQMQAAQKSQDHMPVQLGEDV
seqD.pseudo     ANQIMGNQLSKLPTDMMMSMAGGGSAGAGATIVNPQMRHMHLPGNMKPEHITGP--GLSE
                       :.*:* *  *.     .    *.:  :   :::: .  *.:        * .

seqD.mel.       DVMHPGDVISDMGAVIGCNNNQKTSVQCGSGVGVVTGTTAAG-----------VNVNMH
seqD.virilis    LMPLPADVIGEIGAVMSCNSGQKNNLSCGPQTTAPTAAAASGGPVAGGPGGGGGMNVNMN
seqD.pseudo     EVLLPGDVMTDMG-TAMCNSGQKNSLQCGPAPGVTPVTGAGS-----------INVNMQ
                 :  *.**: ::* .  **..**.:.:.**.    . . : *..           :****:

seqD.mel.       CSSSGAPNGNMMGSSTDMLASFG--NTSCNVIGTAPQMSKEVLNQDSR--THSHQGGVAQ
seqD.virilis    VGMQCSNNPNLMADSPEMMGGPGNTNCVMGIGVGAGAGDKGGIGSQE--AMPLPQGGMAP
seqD.pseudo     GPNSGAPNGNLIGNSSDLLGSFGNTNCGIGIIGTGPDMSKGMPNQLQDGLSQAPQAGMAQ
                   . : * *:: ..*.:::..** *   .:   .  .*   .. .        *.*:*
```


seqD.mel.
seqD.virilis
seqD.pseudo

Sequences used for alignment:

Drosophila melanogaster:

http://www.ncbi.nlm.nih.gov/entrez/viewer.fcgl?db=protein&val=21356901

Drosophila virilis:

http://www.ncbi.nlm.nih.gov/entrez/viewer.fcgl?db=protein&val=89243276

Drosophila psuedoobscura:

http://www.ncbi.nlm.nih.gov/entrez/viewer.fcgl?db=protein&val=54640155

Website used for alignment:

http://www.ch.embnet.org/software/ClustalW.hmtl

Applicants further note, the Examiner states that Venter et al's SEQ ID NO:3129 is 1429 amino acids in length of which amino acids 6-1429 are identical to the "computer readable" form of Applicants' sequence. However, the Examiner contends that Applicants' sequence is only 1464 amino acids long in "paper" form. It is the Examiner's position that amino acids 1140-1179 of the "paper" form of Applicants' sequence is missing in SEQ ID NO:3129 at amino acid positions 1144-1151 of SEQ ID NO:3129. That is, the nucleotides encoding these same amino acids (nucleotides 5482-5601 of SEQ ID NO:1) are missing from the "computer readable" form of Applicants' SEQ ID NO:1. The Examiner concludes that the "paper" copy and the "computer readable" form of SEQ ID NO:1 are not identical.

During a telephone conference with the Examiner on December 7, 2005, the Examiner agreed that, in fact, the "computer readable" form and the "paper" are identical. Thus, this aspect of the Examiner's rejection appear to be moot.

On page 3 of the Office Action, the Examiner notes some informalities which need to be corrected with respect to typographical errors and the lack of sequence identifiers.

Accordingly, Applicants submit herewith a Substitute Specification (and marked-up copy thereof) which incorporates the Examiner's requested amendments.

Additionally, Applicants note that the Examiner's objection to pages 18 and 39 were previously addressed in the Preliminary Amendment filed September 22, 2003.

Furthermore, Applicants are filing simultaneously herewith, a Submission of Replacement Drawings. In light of such, Applicants are hereby amending the specification, as shown in the Substitute Specification, to be consistent with the drawings as filed.

On page 4 of the Office Action, the Examiner requests that Applicants update the status of Parent Application No. 09/915,543.

Accordingly, Applicants hereby incorporate this amendment, as requested by the Examiner, in the Substitute Specification filed herewith.

Further, on page 4 of the Office Action, the Examiner objects to the specification at pages 23, 29 and 41 because it contains hyperlinks. The Examiner contends that the expression "http://" should be removed from the specification.

Accordingly, Applicants hereby incorporate this amendment, as requested by the Examiner, in the Substitute Specification filed herewith.

In addition, on page 4 of the Office Action, the Examiner rejects Claims 61-66 under 35 U.S.C. § 112, second paragraph.

Specifically, the Examiner states that Claims 61 and 62 refer to nucleotide SEQ ID NO:1 as both the nucleic acid encoding and the amino acid sequence depicting dlgs.

Applicants file herewith a substitute Sequence Listing providing a new sequence identifier (SEQ ID NO:23) for the

amino acid sequence, and as a result amend Claim 61 to reference the new sequence identifier, instead of SEQ ID NO:1. Thus, this rejection is now believed to be moot.

Finally, the Examiner states that the Claim 61 refers to amino acids 1-1464 of SEQ ID NO:1 while the computer readable form of the translation of SEQ ID NO:1 depicts only amino acids 1-1429.

As noted above, the Examiner has admitted her error, i.e., the computer readable form also contains amino acids 1-1464.

On page 5 of the Office Action, the Examiner rejects Claims 61-66 under 35 U.S.C. § 112, first paragraph as lacking written description.

Specifically, the Examiner states that there is no support for Claim 65 in the present application, i.e., Claim 65 refers to chimeric polypeptides comprising dlgs and the glutathione-S-transferase, thiroedoxin or an antibody. However, the Examiner contends that the specification, at page 6, paragraph 2, states that the chimeric antibodies will comprise dlgs and an epitope of sequence tag, glutathione-S-transferase, β-galactosidase or alkaline phosphate. That is, the Examiner contends that the inclusion of thioredoxin or an antibody as being part of the chimeric antibody with dLGS is new matter.

For the following reasons, Applicants respectfully traverse the Examiner's rejection.

The Examiner is requested to note that original Claim 21 referred to a chimeric molecule containing the thioredoxin moiety and an antibody. As the original claims are part of the specification as filed, the Examiner's rejection has been rendered moot by the amendment to page 6 of the specification

to include the thioredoxin moiety and an antibody so as to provide antecedent basis.

The Examiner also contends that the specification does not describe variants of the amino acid sequence having at least 90% identity to the amino acid sequence encoded by SEQ ID NO:1 or biologically active fragments.

Applicants hereby amend Claim 61 to recite that the polypeptide has at least 90% sequence identity and the fragment inhibits tcf-driven luciferase activity in colon cancer cells, thereby rendering moot this aspect of the Examiner's rejection.

On page 6 of the Office Action, the Examiner rejects Claims 61-63 and 66 under 35 U.S.C. § 102(e) as being anticipated by Venter et al.

For the following reasons, Applicants respectfully traverse the Examiner's rejection.

As noted above, the present sequence is different in five less amino acids in the beginning of the sequence since the Drosophila sequence has an alternative start codon compared to Venter et al's sequence, and in the additional 40 amino acids not taught in Venter et al.

Accordingly, Applicants respectfully submit that the present invention is not taught or suggested by Venter et al, and thus request withdrawal of the Examiner's rejection.

In view of the amendments to the specification and claims, and the arguments set forth above, reexamination, reconsideration and allowance are respectfully requested.

The Examiner is invited to contact the undersigned at his Washington telephone number on any questions which might arise.

Respectfully submitted,

Gordon Kit
Registration No. 30,764

SUGHRUE MION, PLLC
Telephone: (202) 293-7060
Facsimile: (202) 293-7860

WASHINGTON OFFICE
23373
CUSTOMER NUMBER

Date: May 23, 2006

SUBMISSION OF REPLACEMENT DRAWINGS AND PETITION FOR ACCEPTANCE OF COLOR PHOTOGRAPHS
U.S. Appln. No. 10/664,859

No. 19-4880. Please also credit any overpayments to said Deposit Account. A duplicate copy of this transmittal letter is attached.

Respectfully submitted,

Gordon Kit
Registration No. 30,764

SUGHRUE MION, PLLC
Telephone: (202) 293-7060
Facsimile: (202) 293-7860

WASHINGTON OFFICE
23373
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Date: May 23, 2006